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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,835	07/05/2000	HANS PROPPERT	HARMSEN002	8966

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EXAMINER	
MARX, IRENE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,835	PROPPERT, HANS	
	Examiner	Art Unit	
	Irene Marx	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,8,14,17,19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,8,14,17,19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/14/04 has been entered.

Claims 3, 8, 14, 17, 19 and 21 are being examined on the merits.

Receipt is acknowledged of certified translation of the priority papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No basis or support is found in the present specification for treating or preventing diarrhea mediated by pathogenic fungi in a bovine animal by administering the strain of interest in a therapeutically effective amount for 10 to 13 days. At page 9 of the specification, 300 newborn calves were provided 15.0 ml per calf per day containing a suspension of living *E coli* DSM 6601 without an indication of the number of cells present in the suspension or the percentage of cells that are viable. In addition, there is no clear indication that the calves were exposed to or susceptible to diarrhea mediated by pathogenic fungi at any time. This result cannot be deemed to provide support for the material as now claimed, since there is no clear correlation between the method of treatment and the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 8, 14, 17, 19 and 21 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 17 are vague and indefinite in that the "therapeutically effective amount" required to "prevent" diarrhea or to "prevent" intestinal colonization in all bovine subjects in their lifetime and at any and all conditions is not set forth cannot be determined with sufficient particularity, even when interpreting the claim in light of the specification. As a matter of fact, in the as filed written disclosure the effective amount and time period of "preventing" are not clearly disclosed. At page 9 of the specification, newborn calves were provided 15.0 ml per calf per day containing a suspension of living *E coli* DSM 6601 without an indication of the number of cells present in the suspension or the percentage of cells that are viable. Thus, one of ordinary skill in the art is not apprised of the "therapeutically effective amount" of cells in the suspension required to achieve the results disclosed. In addition, there is no clear indication that the calves were exposed to or susceptible to diarrhea mediated by pathogenic fungi at any time. See also the new matter rejection *supra.*

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

The arguments regarding the period of administration of 10-13 days after birth are noted. However, this is not the material claimed. In addition, even if the objectives outlined in the specification are clear, there is no clear correlation between any data presented and the instant claims regarding the prevention and treatment of diseases "mediated" by pathogenic fungi in bovines. The information pertains only to two species of *Candida.* There is no clear side-by-side comparison and no clear diagnosis pertaining to all pathogenic fungal infection that is "prevented" or "treated".

In response to Applicant's argument that the "therapeutically effective amount" should be read in context with the examples, applicant misinterprets the principle that claims are interpreted in the light of the specification. Although some amounts are disclosed, i.e., that newborn calves were provided 15.0 ml per calf per day containing a suspension of living *E. coli*

DSM 6601, there is no indication of the number of cells present in the suspension or the percentage of cells that are viable. A reading of the specification provides no evidence to indicate that these limitations must be imported into the claims to give meaning to disputed terms. In fact, the "therapeutically effective amount" of *E. coli* DSM 6601, the active ingredient in the suspension is not of record in the as-filed specification.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

Claims 3,8,14, 17, 19 and 21 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over by Hockertz [AT] taken with Lodinova-Zadnikova et al. [AR] for the reasons as stated in the last Office action and the further reasons below.

Hockertz disclose the administration of DSM 6601 (Nissle 1917) to mice. This administration has prophylactic effects on fungi such as *Candida* which are due to immunostimulation (See, e.g., bridging paragraph between pages 795-796). Lodinova-Zadnikova *et al.* disclose the administration of DSM 6601 to humans for intestinal colonization purposes (See, e.g., Abstract and pages 225, 227). This administration has the effect of intestinal colonization and protection of mammals such as humans from diarrhea, which would include fungi-mediated diarrhea.

The references differ from the claimed in that the treatment of bovines is not disclosed. However, the instant written disclosure acknowledges that the process of immuno-stimulation disclosed by Hockertz constitute the same mechanism of action for strain DSM 6601 as the effect of the strain recognized in the instant specification, i.e. that it acts not only by competitive exclusion, but also by increasing the body's endogenous defense mechanisms by immuno-

stimulation (Specification, page 6, paragraph 3). Therefore, one of ordinary skill in the art would have reasonably expected the same effects of competitive exclusion and immuno-stimulation on bovines, and in particular to newborn calves, in view of the beneficial effects disclosed in the cited art of the administration of viable *E.* coli DSM 6601 to other mammals, including newborn humans as taught by Lodinova-Zadnikova *et al.* Since the process as claimed requires the administration of viable *E.* coli DSM 6601, and the prior art cited teaches the administration of identical viable *E.* coli DSM 6601 for the same purposes of competitive exclusion of harmful fungi such as *Candida* as well as protective immunostimulation, one of ordinary skill in the art would have reasonably expected at the time the claimed invention was made that upon administration of viable *E. coli* DSM 6601, the viable bacteria to be effective throughout the body upon colonization regardless of the intended target at the moment of administration.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of preventing and/or treating diarrhea, including fungal diarrhea, of Hockertz [AT] and Lodinova-Zadnikova et al. [AR] by providing viable *E. coli* DSM 6601 in therapeutically effective amounts to bovines, for the expected economic benefit of maximizing the yield of agronomically valuable animals that are healthy and suitable for the production of meat or milk for human consumption.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicant argues that even though the viable *E. coli* DSM 6601 were administered orally in Hockertz, the pathogen *Listeria* or *Candida* was intravenously administered and that no mention is made of gastrointestinal infection. Applicant argues that the mode of infection, i.e., systemic does not cause diarrhea. However, there is no indication that the oral administration of single doses of viable *E. coli* DSM 6601 does not **prevent** diarrhea in this model.

With regard to Lodinova-Zadnikova *et al.* applicant argues that the intent of the reference is to prevent colonization with pathogenic bacteria. However, applicant has not demonstrated that this process did not prevent the colonization with fungi. The taxonomic

differences are well documented, but are irrelevant to a process of "prevention" of diarrhea. It is submitted that one of ordinary skill in the art was not in a position at the time the claimed invention was made to distinguish between the "prevention" of one type of diarrhea and another. That bacteria are more easily combated with antibiotics than fungi is not necessarily the case, in view of the rampant resistant bacterial populations to most antibiotics. Moreover, the mechanism of action of antibiotics is not relevant to the invention as claimed or the references applied.

Applicant's discussion of the differences between monogastric and ruminant digestive tracts is noted. However, this argument is inconsistent in that it fails to consider that the present written disclosure touts the effects of *E.* coli DSM 6601 in newborn calves, which are fed milk exclusively. Thus, a discussion of "indigestible feed" is not material to the results touted. In addition, the contentions regarding Hockertz that the mice are not neonates is not material to the invention as claimed.

Applicants argue that references fail to discuss fungal gut-associated infection and ruminants. However, the claimed method is directed to the oral administration of a strain of *E. coli* known and recognized to colonize the gut and known to be effective in treating fungi such as the yeast *Candida.* It is submitted that one of ordinary skill in the art would have been motivated to administer to bovines, particularly to newborn bovines, a probiotic strain of *E.* coli which is recognized to be safe even in human newborns and which is recognized to colonize the gastrointestinal tract as taught by the references. It must also be remembered that there is no clear indication in the as filed specification of the dosage administered to obtain the touted results.

The scope of the showing must be commensurate with the scope of claims to consider evidence probative of unexpected results, for example. In re Dill, 202 USPQ 805 (CCPA, 1979), In re Lindner 173 USPQ 356 (CCPA 1972), In re Hyson, 172 USPQ 399 (CCPA 1972), In re Boesch, 205 USPQ 215, (CCPA 1980), In re Grasselli, 218 USPQ 769 (Fed. Cir. 1983), In re Clemens, 206 USPQ 289 (CCPA 1980). It should be clear that the probative value of the data is not commensurate in scope with the degree of protection sought by the claim.

Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Irene Marx
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Art Unit 1651